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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,807	07/06/2006	David Paul Humphreys	07-1047-WO-US	6569
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EXAMINER BLANCHARD, DAVID J				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/562,807

Applicant(s)

HUMPHREYS ET AL.

Examiner

David J. Blanchard

Art Unit

1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26, 29 and 30 is/are pending in the application.
- 4a) Of the above claim(s) 19-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 and 29-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/S6108)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☒ Other: Notice to comply

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 March 2009 has been entered.
2. Claims 27-29 have been cancelled.
Claim 1 has been amended.
3. Claims 19-26 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.
4. Claims 1-18 and 29-30 are under consideration.
5. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

6. The rejection of claims 1-7, 10-18 and 27-30 under 35 U.S.C. 102(b) as being anticipated by Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 43 filed 10/10/06) as evidenced by Rodrigues et al (The Journal of Immunology, 151(12), 6954-6961, December 15, 1993, IDS reference 20 filed 10/10/06) is withdrawn in view of the amendments to the claims, i.e., Humphreys does not teach the effector molecules in the presently claimed molecular weight range and in view of the cancellation of claims 27-28.
7. The rejection of claims 1-18, 27-28 and 30 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "derivative" in claims 1 and 27 is withdrawn in view of the amendments to the claims and the cancellation of claims 27-28.
8. The rejection of claims 1-7, 10, 15-18 and 27-30 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 43 filed 10/10/06) is withdrawn in view of the amendments to the claims and the cancellation of claims 27-28.

9. The rejection of claims 1 and 8-9 under 35 U.S.C. 103(a) as being unpatentable over Singh et al (Analytical Biochemistry, 304(2):147-156, May 15, 2002, cited on PTO-892 mailed 3/5/08) in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 42 filed 10/10/06) and Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 43 filed 10/10/06) is withdrawn in view of the New Grounds of Rejections below.

New Grounds of Objections/ Rejections

Sequence Requirements

10. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. The instant application does not contain a paper copy of the "Sequence Listing" as required by 37 C.F.R. 1.821(c). Applicant is reminded to check the entire disclosure to ensure that the application is in sequence compliance.

11. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply (see attached).

12. APPLICANT IS GIVEN THE TIME ALLOTTED IN THIS OFFICE ACTION WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Direct the response to the undersigned.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-7, 10-18 and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al (Nature Biotechnology, 17:780-783, 1999, IDS reference 4 filed 10/10/06) in view of Humphreys et al (Journal of Immunological Methods, 209:193-202, 1997, IDS reference 11 filed 10/10/06).

Chapman et al teach that the random attachment of PEG to Fab' fragments results in conjugate heterogeneity and reduced antigen binding, however, Chapman et al teach that site-specific attachment of PEG molecules (e.g., PEG-maleimide of 5 kDa, 25 kDa and 40 kDa) to

Fab' fragments at one or two engineered hinge cysteine residues retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of one or two defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up and should allow for rapid and economic production of therapeutic antibodies for chronic disease therapy (see entire document, particularly abstract, and pp. 780-781). Chapman et al do not specifically teach wherein the interchain cysteines of the CH1 (residue 233) and CL (residue 214) of the Fab' fragments are mutated to serines or wherein the modified hinge region comprises SEQ ID NO:1, SEQ ID NO:2, or comprises SEQ ID NO:3 or SEQ ID NO:4. These deficiencies are made up for in the teachings of Humphreys et al.

Humphreys et al teach the production of Fab' fragments comprising the hinge sequences of SEQ ID Nos:1, 2 or 3 wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds between hinge regions and other cysteines and removal of the inter CL-CH1 disulfide bond from the Fab' accelerated and simplified the construction of the Fab' fragments and did not affect Fab' stability (see entire document, particularly pp. 194-195, 201 and Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an antibody fragment comprising a Fab' fragment in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the antibody fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID Nos:1, 2 or 3) for PEGylation as well as pharmaceutical compositions comprising said antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer for chronic disease therapy.

One of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have produced an antibody fragment comprising a Fab' fragment in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the antibody fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID Nos:1, 2 or 3) for PEGylation as well as pharmaceutical compositions comprising said antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer for chronic disease therapy in view of Chapman et al

and Humphreys et al because Chapman et al teach that the random attachment of PEG to Fab' fragments results in conjugate heterogeneity and reduced antigen binding, however, the site-specific attachment of PEG molecules (e.g., PEG-maleimide of 5 kDa, 25 kDa and 40 kDa) to Fab' fragments at one or two engineered hinge cysteine residues retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of one or two defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up and should allow for rapid and economic production of therapeutic antibodies for chronic disease therapy and Humphreys et al teach the production of Fab' fragments comprising the hinge sequence of SEQ ID Nos:1, 2 or 3 wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds between the hinge regions and other cysteines and removal of the inter CL-CH1 disulfide bond from the Fab' accelerated and simplified the construction of the Fab' fragments and did not affect Fab' stability. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce site-specific PEGylated Fab' fragments wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds, to simplify and accelerate the construction of the Fab' fragments using the hinge peptides of Humphreys (e.g., identical to SEQ ID Nos:1, 2 or 3) for PEG attachment since site-specific attachment of PEG molecules at one or two hinge cysteine(s) retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of one or two defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up, allowing for rapid and economic production of therapeutic antibodies for chronic disease, thereby overcoming conjugate heterogeneity and reduced antigen binding associated with random attachment of PEG to Fab' fragments according to Chapman et al. Thus, there would be several advantages to producing antibody fragments comprising a Fab' fragment lacking the interchain CL-CH1 cysteines and modified by site-specific attachment of at least one PEG molecule at the cysteine residue(s) within the hinge peptide of SEQ ID NO:1, 2 or 3. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by

their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Chapman et al provides evidence that site-specific attachment of PEG molecules to hinge cysteines of Fab' fragments does not reduce antigen binding and removal of the inter CL-CH1 disulfide bond accelerated and simplified the construction of the Fab' fragments and did not affect Fab' stability. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced an antibody fragment comprising a Fab' fragment in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the antibody fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID Nos:1, 2 or 3) for PEGylation as well as pharmaceutical compositions comprising said antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer for chronic disease therapy in view of Chapman et al and Humphreys et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 1 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al (Analytical Biochemistry, 304(2):147-156, May 15, 2002, cited on PTO-892 mailed 3/5/08) in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 42 filed 10/10/06) and Humphreys et al (Journal of Immunological Methods, 209:193-202, 1997, IDS reference 11 filed 10/10/06).

Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and selenol-catalyzed reduction of disulfide bonds in Fab fragments has previously been reported (see entire document, particularly abstract, pp, 148, 154-155 and Fig. 1). Singh et al do not specifically teach an antibody

comprising a Fab' fragment comprising a hinge region containing one or two cysteines and wherein the Fab' fragment has been modified by attachment of at least one PEG or PEG derivative wherein both the interchain cysteine of CL and the interchain cysteine of CH1 have been replaced with another amino acid such that the heavy chain in the fragment is not covalently bonded to the light chain. These deficiencies are made for in the teachings of Hesi et al and Humphreys.

Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')₂ (e.g., antibody fragment comprising Fab') fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules, and wherein the disulfide bridge linking the heavy and light chains is avoided by substituting the cysteine residue of the heavy or light chain with serine and the PEG molecules are attached via a cysteine residue or residues engineered into a selected site or selected sites in the antibody fragment as well as pharmaceutical compositions comprising the anti-IL-8 antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer (see entire document, particularly pp. 20, lines 29-37, pp. 21-27, 37-38, 42, 98-102 and 104-105).

Humphreys et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')₂ fragments in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the anti-IL-8 Fab, Fab', Fab-SH and F(ab')₂ fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID No:1, 2 or 3) as well as a cysteine residue or residues engineered into a selected site or sites in the antibody fragment (i.e., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides as taught by Singh et al for therapeutic benefit of inflammatory disorders.

One of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')₂ fragments in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the anti-IL-8 Fab, Fab', Fab-SH and F(ab')₂ fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID No:1, 2 or 3) as well as a cysteine residue or residues engineered into a selected site or sites in the antibody fragment (i.e.,

in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys et al because Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')₂ (e.g., antibody fragment comprising Fab') fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules, and wherein the disulfide bridge linking the heavy and light chains is avoided by substituting the cysteine residue of the heavy or light chain with serine and the PEG molecules are attached via a cysteine residue or residues engineered into a selected site or selected sites in the antibody fragment and Humphreys et al teach the production of Fab' fragments comprising the hinge sequences of SEQ ID Nos:1, 2 or 3 wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds between hinge regions and other cysteines and removal of the inter CL-CH1 disulfide bond from the Fab' accelerated and simplified the construction of the Fab' fragments and did not affect Fab' stability. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce anti-IL-8 Fab, Fab', Fab-SH and F(ab')₂ fragments lacking the CL-CH1 interchain disulfide and comprising a hinge peptide containing one or two cysteines (e.g., SEQ ID No:1, 2 or 3) as well as cysteine residues engineered into selected sites in the antibody fragment (e.g., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides as taught by Singh et al since selenol-catalyzed reduction of interchain disulfides provides a rapid method in which the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and the method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established

scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Singh et al provides evidence that reduction of interchain disulfide bonds of an antibody does not result in a significant decrease in affinity or stability and selenol-catalyzed reduction of disulfide bonds in Fab fragments has been performed previously (Singh et al, pg. 148 1st col.). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')₂ fragments in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the anti-IL-8 Fab, Fab', Fab-SH and F(ab')₂ fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID No:1, 2 or 3) as well as a cysteine residue or residues engineered into a selected site or sites in the antibody fragment (i.e., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-7, 10-11, 13, 15-18 and 29-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of Chapman et al (Nature Biotechnology, 17:780-783, 1999, IDS reference 4 filed 10/10/06) and Humphreys et al (Journal of Immunological Methods, 209:193-202, 1997, IDS reference 11 filed 10/10/06).

Claims 7 and 10 of U.S. Patent No. 6,642,356 B1 are drawn to a Fab or Fab' fragment comprising one polypeptide chain that comprises the amino acid sequence of SEQ ID NO:1 (e.g., TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the Fab or Fab' fragment has one or more effector or reporter molecules attached to it. Claims 7 and 10 of U.S. Patent No. 6,642,356 B1 do not specifically teach wherein the interchain cysteines of the CH1 and CL are substituted with serine and wherein the effector molecule is PEG, or pharmaceutical compositions comprising the Fab or Fab' fragment and a pharmaceutically acceptable carrier or excipient. These deficiencies are made up for in the teachings of Chapman et al and Humphreys et al.

Chapman et al have been described supra.

Humphreys have been described supra.

The claims in the instant application are obvious variants of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a Fab or Fab' fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the CH1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for chronic disease therapy.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a Fab or Fab' fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the C_H1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for chronic disease therapy in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Chapman et al and Humphreys et al because Chapman et al teach that the random attachment of PEG to Fab' fragments results in conjugate heterogeneity and reduced antigen binding, however, site-specific attachment of PEG molecules (e.g., PEG-maleimide of 5 kDa, 25 kDa and 40 kDa) to Fab' fragments at engineered hinge cysteine residues retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up and should allow for rapid and economic production of therapeutic antibodies for chronic disease therapy according to Chapman et al and Humphreys et al teach the production of Fab' fragments wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds between hinge regions and other cysteines and removal of the inter CL-CH1 disulfide bond from the Fab' accelerated and simplified the construction of the Fab' fragments and did not affect Fab' stability. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce a Fab or Fab' fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the C_H1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for immunotherapy since site-specific attachment of PEG molecules at hinge cysteines retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up, allowing for rapid and economic production of therapeutic antibodies for chronic disease, thereby

overcoming conjugate heterogeneity and reduced antigen binding associated with random attachment of PEG to Fab' fragments according to Chapman et al. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a Fab or Fab' fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the C_H1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for chronic disease therapy in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Chapman et al and Humphreys et al.

Claims 1-7, 10-11, 13, 15-18 and 29-30 are directed to an invention not patentably distinct from claims 7 and 10 of commonly assigned U.S. Patent No. 6,642,356 B1. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,642,356 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

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18. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643